AMENDMENTS TO THE SPECIFICATION

Please amend page 23, lines 24-29 as follows:

-- HPV16-E6 PROTEIN SEQUENCE

001 MHQKRTAMFQ DPQERPRKLP QLCTELQTTI HDIILECVYC KQQLLRREVY DFAFRDLCIV

061 YRDGNPYAVC DKCLKFYSKI SEYRHYCYSL YGTTLEQQYN KPLCDLLIRC INCQKPLCPE

121 EKQRHLDKKQ RFHNIRGRWT GRCMSCCRSS RTRRETQL

(SEQ ID NO: 2) --

Please amend page 23, line 35 to page 24, line 1 as follows:

-- Four fragments selected for peptide synthesis to obtain full length HPV16E6 synthetic protein:

01: 001-039 MHQKRTAMFQDPQERPRKLPQLCTELQTTIHDIILECVY-SR

02: 040-072 X-CKQQLLRREVYDFAFRDLCIVYRDGNPYAVCDK-SR

03: 073-117 X-CLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINCQKPL-SR

04: 118-158 CPEEKQRHLDKKQRFHNIRGRWTGRCMSCCRSSRTRR ETQL-OH

(SEQ ID NO: 2) --

Please Amend page 24, lines 11-44 as follows:

-- HPV16-E2 PROTEIN SEQUENCE

001 METLCQRLNV CQDKILTHYE NDSTDLRDHI DYWKHMRLEC AIYYKAREMG FKHINHQVVP

061 TLAVSKNKAL QAIELQLTLE TIYNSQYSNE KWTLQDVSLE VYLTAPTGCI KKHGYTVEVQ

121 FDGDICNTMH YTNWTHIYIC EEASVTVVEG QVDYYGLYYV HEGIRTYFVQ FKDDAEKYSK

181 NKVWEVHAGG QVILCPTSVF SSNEVSSPEI IRQHLANHPA ATHTKAVALG TEETQTTIQR

241 PRSEPDTGNP CHTTKLLHRD SVDSAPILTA FNSSHKGRIN CNSNTTPIVH LKGDANTLKC

301 LRYRFKKHCT LYTAVSSTWH WTGHNVKHKS AIVTLTYDSE WQRDQFLSQV KIPKTITVST

361 GFMSI

(SEQ ID NO: 3)

Seven fragments selected for peptide synthesis to obtain full length HPV16 E2 synthetic protein:

01: 001-039 METLCQRLNVCQDKILTHYENDSTDLRDHIDYWKHMRLE-SR

02: 040-108 X-CAIYYKAREMGFKHINHQVVPTLAVSKNKALQAIEL QLTLETIYNSQYSNE KWTLQDVSLEVYLTAPTG-SR

03: 109-139 X-CIKKHGYTVEVQFDGDICNTMHYTNWTHIYI-SR

04: 140-194 X-CEEASVTVVEGQVDYYGLYYVHEGIRTYFVQFKDDAEKYSKNK VWEVHAGGQVIL-SR

05: 195-250 X-CPTSVFSSNEVSSPEIIRQHLANHPAATHTKAVALGTEETQTTIQR PRSEPDTGNP-SR

06: 251-299 X-CHTTKLLHRDSVDSAPILTAFNSSHKGRINCNSNTTPIVHLKGD ANTLK-SR

07: 300-365 CLRYRFKKHCTLYTAVSSTWHWTGHNVKHKSAIVTLTYDSEWQRDQFLSQV KIPKTITVSTGFMSI

(SEQ ID NO: 3) --

Please amend page 25, lines 15-39 as follows:

-- PART 1: 001-210

01:001-039 METLCQRLNV CQDKILTHYE NDSTDLRDHI DYWKH MRLE-SR

02:040-108 X-CAIYYKAREMGFKHINGQVVPTLAVSKNKALQAIEL QLTLE TIYNSQYSNEKWTLQDVSLEYLTAPTG-SR

03:109-155 X-CIKKHGYTVEVQFDGDICNTMHYTNWTHIYICEEASVTVVEG QVDYY-SR

04:156-210 XX-GLYYVHEGIRTYFVQFKDDAEKYSKNKVWEVHAGG QVILCPTSVF SSNEVSSPEI

PART 2: 190-365

01:190-229 GQVILCPTSVFSSNEVSSPEIIRQHLANHPAATHTKAV AL-SR

02:230-280 XXGTEETQTTIQRPRSEPDTGNPCHTTKLLHRDSVDSA PILTA FNSSHKGRIN-SR

03:281-308 X-CNSNTTPIVHLKGDANTLKCLRYRFKKH-SR

04:309-365 CTLYTAVSSTWHWTGHNVKHKSAIVTLTYDSEWQRDQF LSQV KIPKTITVSTGFMSI

(SEQ ID NO: 3) --

Please amend page 26, lines 9-46 as follows:

-- Example 4: Chemical Synthesis of HPV18 E7

HPV18-E7 PROTEIN SEQUENCE

01 MHGPKATLQD IVLHLEPQNE IPVDLLCHEQ LSDSEEENDE IDGVNHQHLP ARRAEPQRHT

61 MLCMCCKCEA RIELVVESSA DDLRAFQQLF LNTLSFVCPW CASQQ

(SEQ ID NO: 4)

Two fragments selected for peptide synthesis to obtain full length HPV18 E2 synthetic protein, details identical to example 1:

01:001-065 MHGPKATLQDIVLHLEPQNEIPVDLLCHEQLSDSEEEN DEIDGVNHQHLP ARRAEPQRHT MLCMC-SR

02:066-~~099~~105 CKCEA RIELVVESSA DDLRAFQQLF LNTLSFVCPW CASQQ

(SEQ ID NO: 4)

Example 5: Chemical Synthesis of HPV18 E6

HPV18-E6 PROTEIN SEQUENCE

001 MARFEDPTRR PYKLPDLCTE LNTSLQDIEI TCVYCKTVLE LTEVFEFAFK DLFVVYRDSI

061 PHAACHKCID FYSRIRELRH YSDSVYGDTL EKLTNTGLYN LLIRCLRCQK PLNPAEKLRH

121 LNEKRRFHNI AGHYRGQCHS CCNRARQERL QRRRETQV

(SEQ ID NO: 5)

Four fragments selected for peptide synthesis to obtain full length HPV18 E6 synthetic protein:

01:001-034 MARFEDPTRRPYKLPDLCTELNTSLQDIEITCVY-SR

02:035-064 X-CKTVLELTEVFEFAFKDLFVVYRDSIPHAA-SR

03:065-104 X-CHKCIDFYSRIRELRHYSDSVYGDTLEKLTNTGLYN LLIR-SR

04:105-158 CLRCQKPLNPAEKLRHLNEKRRFHNIAGHYRGQCHSCC NRARQERL

QRRRETQV

(SEQ ID NO: 5) --

Please amend page 27, lines 6-41 as follows:

-- Example 6: Chemical Synthesis of HPV18 E2

HPV18-E2 PROTEIN SEQUENCE

001 MQTPKETLSE RLSCVQDKII DHYENDSKDI DSQIQYWQLI RWENAIFFAA REHGIQTLNH

061 QVVPAYNISK SKAHKAIELQ MALQGLAQSR YKTEDWTLQD TCEELWNTEP THCFKKGGQT

121 VQVYFDGNKD NCMTYVAWDS VYYMTDAGTW DKTATCVSHR GLYYVKEGYN TFYIEFKSEC

181 EKYGNTGTWE VHFGNNVIDC NDSMCSTSDD TVSATQLVKQ LQHTPSPYSS TVSVGTAKTY

241 GQTSAATRPG HCGLAEKQHC GPVNPLLGAA TPTGNNKRRK LCSGNTTPII HLKGDRNSLK

301 CLRYRLRKHS DHYRDISSTW HWTGAGNEKT GILTVTYHSE TQRTKFLNTV AIPDSVQILV

361 GYMTM

(SEQ ID NO: 6)

Seven fragments selected for peptide synthesis to obtain fill length HPV18 E2 synthetic protein:

01:001-013 MQTPKETLSERLS-SR

02:014-101 X-CVQDKIIDHYENDSKDIDSQIQYWQLIRWENAIFFAAREHGIQTLNH QVVPAYNISKSKAHKAIELQMALQGLA QSRYKTEDWTLQDT-SR

03:102-155 X-CEELWNTEPTHCFKKGGQTVQVYFDGNKDNCMTYVA WDS VYYMTDAGTWDKTAT-SR

04:156-199 X-CVSHRGLYYVKEGYNTFYIEFKSECEKYGNTGTWEVHFGNNVID-SR

05:200-251 X-CNDSMCSTSDDTVSATQLVKQLQHTPSPYSSTVSVGTAKTY GQTSAATRPGH-SR

06:252-300 X-CGLAEKQHCGPVNPLLGAATPTGNNKRRKLCSGNTTPIIHLKGD RNSLK-SR

07:301-365 X-CLRYRLRKHSDHYRDISSTWHWTGAGNEKTGILTVTYHSE TQRTKFLNTVAIPDSVQILVGYMTM

(SEQ ID NO: 6) --

Please amend page 28, lines 6-31 as follows:

-- PART 1: 001-210

01:001-053 MQTPKETLSERLSCVQDKIIDHYENDSKDIDSQIQYWQLI RWENAIFFAAREH-SR

02:054-112 XX-GIQTLNHQVVPAYNISKSKAHKAIELQMALQGLAQ SRYKTEDWTLQD TCEELWNTEPTH-SR

03:113-155 X-CFKKGG VQVYFDGNKD NCMTYVAWDS VYYMTDAGTW DKTAT-SR

04:156-210 X-CVSHRGLYYVKEGYN TFYIEFKSEC EKYGNTGTWE VHFGNNVIDC NDSMCSTSDD

PART 2: 191-365

01:191-251 VHFGNNVIDCNDSMCSTSDDTVSATQLVKQLQHTPSPYSS TVSVGTAKTYGQTSAATRPGH-SR

02:252-300 X-CGLAEKQHCGPVNPLLGAATPTGNNKRRKLCSGNTT PIIHLKGD RNSLK-SR

03:301-365 X-CLRYRLRKHSDHYRDISSTWHWTGAGNEKTGILTVTYHSE TQRTKFLNTVAIPDSVQILVGYMTM

(SEQ ID NO: 6) --

Please amend page 28, line 41 to page 29, line 7 as follows:

-- Control antigens and adjuvants. Two peptides were generated, the H-2D^{b}-restricted CTL epitope HPV16-E7$_{49-57}$ (RTF) and the E7$_{43-77}$ 35 residue long peptide GQAEPDRAHYNIVTFCCKCDSTLRLCVQSTHVDIR (SEQ ID NO: 7). The purity of the peptides was determined by RP-HPLC and was found to be routinely over 90% pure. Peptides were dissolved in 0.5% DMSO in PBS and, if not used immediately, stored at -20°C. The recombinant was produced in recombinant E. coli transformed with Pet-19b-HPV16-E7 and purified as described previously (De Bruijn, M. L. et al., Cancer Res. 58 p 724-31, 1999). CpG-oligodeoxynucleotides (ODN) 1826, sequence TTCATGACGTTCCTGACGTT (SEQ ID NO: 8), were provided by Coley Pharmaceutical and used at a working concentration of 50 µg/mouse (Zwaveling S. et al., J. Immunol. 169, p350-8, 2002). --

Please amend the paragraph at page 30, line 16 to page 31, line 15 as follows:

-- Since numerous studies show that: (1) protection of C57BL/6 mice against HPV16-E7-expressing tumors is largely dependent on E7$_{49-57}$-specific CD8+ T cells (De Bruijn M. L. et al., Cancer Res. 58, p 724-31, 1998, Greenstone H. L. et al., PNAS 95, p 1800-5, 1998, Lin K. Y. et al., Cancer Res. 56, p21-6, 1996, Feltkamp M. C. et al., Eur. J. Immunol. 23, p 2242-9,, 1993), and (2) that the ability of HPV16-E7-specific T-cells to protect against tumor development or to

eradicate established tumors is correlated with the percentage of $E7_{49-57}$-tetramer positive CD8+ T-cells (Van der Burg et al., Vaccine 19, p 3652-60, 2001), the antigenicity of synthetic HPV16-E7 protein was assessed by its capacity to induce such HPV16-$E7_{49-57}$-specific CD8+ T-cells. C57BL/6 mice were injected with several vaccines that have been used successfully in the past, including the minimal CTL epitope ($E7_{49-57}$: RAHYNIVTF (SEQ ID NO: 9)), a longer peptide CE743-77) that was known to induce vigorous $E7_{49-57}$-specific CD8+ T-cell responses, recombinant HPV16-E7 or the synthetic HPV16-E7 protein at equimolar concentrations of the minimal CTL epitope, in combination with CpG. Ten days following vaccination, the spleens were harvested and the cells directly analysed by H2-D.sup.b $E7_{49-57}$ (RAHYNIVTF)-tetramer staining (Van der Burg S. H. Vaccine 19, p 3652-60, 2001) (FIG. 3a) as well as subjected to an extra round of in vitro stimulation, which magnifies but does not alter the hierarchy of in vivo induced CD8+ T cell responses, before the percentage of $E7_{49-57}$ peptide-specific CD8+ T-cells was determined (FIG. 3b). As expected, the longer E7 peptide was able to induce strong HPV16-E7-specific CD8+ T-cells at a high antigen dose as well as at the lower dose, whereas the response induced by the minimal CTL epitope was significantly lower. Importantly, the HPV16-E7-specific CD8+ T-cell response induced by one single injection of synthetic E7 protein was comparable to that of the recombinant HPV16-E7 protein and somewhat higher than the other vaccines. To confirm that functional CD8+ T-cell responses were triggered following a single vaccination with the synthetic E7 protein, the numbers of INF-γ-producing $CD8^+$ cells were measured upon stimulation with dendritic cells (DC) only, or pulsed with either the long $E7_{43-77}$ peptide or the recombinant E7 protein. High numbers of INFγ-producing $CD8^+$ T-cells were detected in the spleens of mice vaccinated with the synthetic E7 protein, confirming that the $CD8^+$ T-cells detected by the H2-D^b $E7_{49-57}$-tetramers were functionally active (FIG. 4). Furthermore, the CD8+ T-cells from these mice reacted against recombinant E7 protein-pulsed DC, indicating that the synthetic HPV16-E7 protein retained its full antigenic potential. --